

CLAIMS

1. A method of treating Type 1 Diabetes in a mammal suffering from Type 1 Diabetes  
5 comprising administering to the mammal a therapeutically effective amount of a selective  
PDE5 inhibitor, without substantial PDE2 inhibiting activity, or a pharmaceutically acceptable  
salt thereof, or a pharmaceutical composition containing either entity.

2. The method according to Claim 1 wherein the PDE5 inhibitor is selected from  
sildenafil, tadalafil, vardenafil, DA-8159 and 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)  
10 pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

3. The method according to Claim 1 or 2 further comprising one or more additional  
active agents selected from NO-agonist compounds or NO synthase substrates; potassium  
channel modulators; angiotensin receptor antagonists; antilipemic agents; antiplatelet or  
antithrombotic agents; acetylcholinesterase inhibitors; estrogen receptor modulators, agonists  
15 or antagonists; PDE inhibitors; NEP inhibitors; angiotensin-converting enzyme inhibitors or  
neutral endopeptidase; calcium-channel blockers; protein kinase C- $\beta$ -inhibitors; activators of  
AMP-activated protein kinase; insulin; weight loss agents; dipeptidyl peptidase IV inhibitors;  
glucagon antagonists; inhibitors of PTP1B; reducers of PTP1B using antisense technology;  
glycogen synthase kinase-3 inhibitors; GLP-1 agonists; PPAR-gamma agonists; PPAR-alpha  
20 agonists; PPAR-alpha/PPAR-gamma agonists; sorbitol dehydrogenase inhibitors; reductase  
inhibitors; and soluble guanylyl cyclase activators.

4. The method according to Claim 3 wherein the active agent is selected from insulin,  
raloxifene, lasofoxifene, (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-  
tetrahydronaphthalene-2-ol, atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin,  
25 itavastatin, simvastatin and (+)-(3R,5S)-bis-(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-  
methanesulfonylamino)-pyrimidin-5-yl)-3,5-dihydroxy-6(E)-heptenoic acid.

5. The method according to Claim 4 wherein the PDE5 inhibitor is sildenafil.

6. The method according to Claim 4 wherein the agent is insulin,

7. The method according to Claim 4 wherein the agent is raloxifene.

8. The method according to Claim 4 wherein the agent is lasofoxifene.

9. The method according to Claim 4 wherein the agent is (-)-cis-6-phenyl-5-[4-(2-  
pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol.

10. The method according to Claim 4 wherein the agent is atorvastatin.

11. The method according to Claim 4 wherein the agent is cerivastatin.

12. The method according to Claim 4 wherein the agent is fluvastatin.

13. The method according to Claim 4 wherein the agent is lovastatin.

14. The method according to Claim 4 wherein the agent is pravastatin.

15. The method according to Claim 4 wherein the agent is itavastatin.

5 16. The method according to Claim 4 wherein the agent is simvastatin.

17. The method according to Claim 4 wherein the agent is (+)-(3R,5S)-bis-(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-pyrimidin-5-yl)-3,5-dihydroxy-6(E)-heptenoic acid.

18. A pharmaceutical combination for the treatment of Type 1 Diabetes in an  
10 individual comprising an effective amount of a PDE5 inhibitor, without substantial PDE2  
inhibiting activity, or a pharmaceutically acceptable salt thereof and one or more additional  
active agents selected from NO-agonist compounds or NO synthase substrates; potassium  
channel modulators; angiotensin receptor antagonists; antilipemic agents; antiplatelet or  
antithrombotic agents; acetylcholinesterase inhibitors; estrogen receptor modulators, agonists  
15 or antagonists; PDE inhibitors; NEP inhibitors; angiotensin-converting enzyme inhibitors or  
neutral endopeptidase; calcium-channel blockers; protein kinase C- $\beta$ -inhibitors; activators of  
AMP-activated protein kinase; insulin; weight loss agents; dipeptidyl peptidase IV inhibitors;  
glucagons antagonists; inhibitors of PTP1B; reducers of PTP1B using antisense technology;  
glycogen synthase kinase-3 inhibitors; GLP-1 agonists; PPAR-gamma agonists; PPAR-alpha  
20 agonists; PPAR-alpha/PPAR-gamma agonists; sorbitol dehydrogenase inhibitors; reductase  
inhibitors; and soluble guanyl cyclase activators.

19. The pharmaceutical combination of Claim 18 wherein the PDE5 inhibitor is  
selected from sildenafil, tadalafil, vardenafil, DA-8159 and 5-[2-ethoxy-5-(4-ethylpiperazin-1-  
ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-  
25 7-one

20. The pharmaceutical combination according to Claim 18 or 19 wherein the  
additional active ingredient is selected from antilipemic agents; estrogen receptor  
modulators, agonists and antagonists; and insulin.

21. The pharmaceutical combination according to Claim 20 wherein the active  
30 ingredient is selected from insulin, raloxifene, lasofoxifene, (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-  
1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol, atorvastatin, cerivastatin,  
fluvastatin, lovastatin, pravastatin, itavastatin, simvastatin and (+)-(3R,5S)-bis-(7-(4-(4-  
fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-pyrimidin-5-yl)-3,5-  
dihydroxy-6(E)-heptenoic acid.

35 22. The combination according to Claim 21 wherein the agent is insulin,

23. The combination according to Claim 21 wherein the agent is raloxifene.
24. The combination according to Claim 21 wherein the agent is lasofoxifene.
25. The combination according to Claim 21 wherein the agent is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol.
- 5 26. The combination according to Claim 21 wherein the agent is atorvastatin.
27. The combination according to Claim 21 wherein the agent is cerivastatin.
28. The combination according to Claim 21 wherein the agent is fluvastatin.
29. The combination according to Claim 21 wherein the agent is lovastatin.
30. The combination according to Claim 21 wherein the agent is pravastatin.
- 10 31. The combination according to Claim 21 wherein the agent is itavastatin.
32. The combination according to Claim 21 wherein the agent is simvastatin.
33. The combination according to Claim 21 wherein the agent is (+)-(3R,5S)-bis-(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-pyrimidin-5-yl))-3,5-dihydroxy-6(E)-heptenoic acid.
- 15 34. A kit for the treatment of Type 1 diabetes comprising a PDE5 inhibitor, without substantial PDE2 inhibiting activity, or a pharmaceutically acceptable salt thereof, in an effective amount, optionally one or more pharmaceutically acceptable carrier, excipient or diluent, and one or more of:
- 20 a. means for testing for Type 1 diabetes;
- b. one or more additional active agents selected from NO-agonist compounds or NO synthase substrates; potassium channel modulators; angiotensin receptor antagonists; antilipemic agents; antiplatelet or antithrombotic agents; acetylcholinesterase inhibitors; estrogen receptor modulators, agonists or antagonists; PDE inhibitors; NEP inhibitors; angiotensin-converting enzyme
- 25 inhibitors or neutral endopeptidase; calcium-channel blockers; protein kinase C- $\beta$ -inhibitors; activators of AMP-activated protein kinase; insulin; weight loss agents; dipeptidyl peptidase IV inhibitors; glucagons antagonists; inhibitors of PTP1B; reducers of PTP1B using antisense technology; glycogen synthase kinase-3
- 30 inhibitors; GLP-1 agonists; PPAR-gamma agonists; PPAR-alpha agonists; PPAR-alpha/PPAR-gamma agonists; sorbitol dehydrogenase inhibitors; reductase inhibitors; and soluble guanyl cyclase activators; and/or
- c. instructions for the treatment of Type 1 diabetes.
- 35 35. The kit of claim 34 wherein the PDE5 inhibitor is sildenafil, tadalafil, vardenafil, DA-8159 or 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

36. The kit of claim 35 wherein the PDE5 inhibitor is sildenafil.

37. The kit of Claims 34, 35 or 36 wherein the additional active agent is selected from: insulin, raloxifene, lasofoxifene, (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol, atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, itavastatin, simvastatin and (+)-(3R,5S)-bis-(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-pyrimidin-5-yl)-3,5-dihydroxy-6(E)-heptenoic acid.

38. The kit according to Claim 37 wherein the agent is insulin,

39. The kit according to Claim 37 wherein the agent is raloxifene.

40. The kit according to Claim 37 wherein the agent is lasofoxifene.

41. The kit according to Claim 37 wherein the agent is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol.

42. The kit according to Claim 37 wherein the agent is atorvastatin.

43. The kit according to Claim 37 wherein the agent is cerivastatin.

44. The kit according to Claim 37 wherein the agent is fluvastatin.

45. The kit according to Claim 37 wherein the agent is lovastatin.

46. The kit according to Claim 37 wherein the agent is pravastatin.

47. The kit according to Claim 37 wherein the agent is itavastatin.

48. The kit according to Claim 37 wherein the agent is simvastatin.

49. The kit according to Claim 37 wherein the agent is (+)-(3R,5S)-bis-(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-pyrimidin-5-yl)-3,5-dihydroxy-6(E)-heptenoic acid.